Enteric (typhoid and paratyphoid) fever

Rebecca Kuehn, Paul Rahden, Huma Syed Hussain, Abhilasha Karkey, Farah Naz Qamar, Priscilla Rupali, Christopher M Parry

Enteric fever, caused by the human-restricted bacteria *Salmonella enterica* serovar Typhi (typhoid) and *Salmonella enterica* serovar Paratyphi A, B, and C (paratyphoid), affects persons residing in, or travelling from, areas lacking safe water, sanitation, and hygiene infrastructure. Transmission is by the faecal–oral route. A gradual fever onset over 3–7 days with malaise, headache, and myalgia is typical. Symptoms can be altered by previous antimicrobial use. Life-threatening complications can arise in the second week of untreated illness. Differentiation from other febrile illnesses is challenging. Blood or bone marrow culture remain reference standard diagnostic methods, despite the low sensitivity of blood culture. Azithromycin, ciprofloxacin (excepting cases originating in south Asia due to drug resistance), or ceftriaxone are recommended treatment options for both typhoid and paratyphoid; however, choice should be guided by local resistance patterns. Ciprofloxacin-resistant and ceftriaxone-resistant typhoid is common in Pakistan. Three vaccine types are available for prevention of typhoid disease, including the newer, more effective typhoid Vi-conjugate vaccines. Vaccination as well as water, sanitation, and hygiene measures are cornerstones of prevention.

Published **Online**
September 3, 2025
https://doi.org/10.1016/S0140-6736(25)01335-2

Cochrane Infectious Diseases Group, Department of Clinical Sciences, Liverpool School of Tropical Medicine, Liverpool, UK (R Kuehn MD)**; Department of Implementation Research, Bernhard Nocht Institute for Tropical Medicine, Hamburg, Germany** (P Rahden MD)**; Department of Pediatrics and Child Health, Aga Khan University, Karachi, Pakistan** (H S Hussain MD, F N Qamar FRCP)**; Oxford University Clinical Research Unit, Kathmandu, Nepal** (A Karkey DPhil)**; Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, University of Oxford, Oxford, UK** (A Karkey, C M Parry FRCP)**; Department of Infectious Diseases, Christian Medical College, Vellore, India** (P Rupali MD)**; Department of Clinical Sciences, Liverpool School of Tropical Medicine, Liverpool** (C M Parry)

Correspondence to:
Dr Christopher M Parry, Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, University of Oxford, Oxford OX3 7LF, UK
christopher.parry@ndm.ox.ac.uk

Introduction

Enteric fever is an invasive infection caused by the human-restricted pathogens *Salmonella enterica* serovar Typhi (*S* Typhi; typhoid fever) and *Salmonella enterica* serovar Paratyphi A and occasionally Paratyphi B and C (*S* Paratyphi; paratyphoid fever).[1] Among populations in low-income and middle-income countries (LMICs) that lack access to safe drinking water, sanitation, and hygiene (WASH) infrastructure enteric fever is an important cause of febrile illness, causing morbidity, mortality, and an economic burden for families.[2,3] The Global Burden of Disease Study estimated 9·3 million cases of enteric fever globally in 2021.[4] The prevalence of enteric fever remains high in Asia and Africa, with an estimated 62% of the global burden in south Asia (figure 1). The global mortality in 2021 was estimated at more than 100 000 deaths each year.[4] These estimates are constrained by the limited data availability in LMICs.

Public health approaches to reduce the disease burden of enteric fever in LMICs include access to WASH and the introduction of typhoid Vi-conjugate vaccines.[5,6] Despite these steps, enteric fever remains an important cause of acute undifferentiated fever among patients in LMICs, and in returned travellers with fever from endemic areas.[2,7] Case management is challenging because the clinical presentation overlaps with other infections, diagnostic tests are unsatisfactory, and widespread antimicrobial resistance has narrowed treatment options.[8–11] This Seminar focuses on the evidence supporting effective case management of patients with suspected enteric fever.

The bacteria

S Typhi and *S* Paratyphi A, B, and C are motile Gram-negative bacteria and serovars of *Salmonella* species in the family Enterobacteriaceae. The genome of *S* Typhi contains pathogenicity islands with virulence-associated genes such as the Vi capsular antigen, flagella antigens, and type III secretion systems.[12,13] A typhoid toxin has been described, but its role in disease pathophysiology is unclear.[14,15] Humans are the sole reservoir of this infection. Genomic comparisons with non-typhoidal salmonella show areas of genome loss and inactive pseudogenes in *S* Typhi and *S* Paratyphi that are consistent with evolutionary adaption to a narrow human niche.[12,16] Genomic types vary in different global regions.[17–20] The haplotype H58 (clade 4.3.1 and derived genotypes) has been associated with the spread of antimicrobial resistance from south Asia to other regions such as east Africa.[17,20]

How do people acquire infection?

The disease is transmitted by the faecal–oral route through ingestion of food or water contaminated by human faeces or urine containing the bacterium *S* Typhi or *S* Paratyphi.[21] Transmission can occur by a short-cycle, in which faecal shedding of the bacteria in the immediate environment contaminates food and water because of

Search strategy and selection criteria

We searched MEDLINE (OVID), Embase (OVID), Global Index Medicus, and—from Web of Science—Science Citation Index Expanded (SCI-EXPANDED), Social Sciences Citation Index (SSCI), Conference Proceedings Citation Index–Science (CPCI-S), and Conference Proceedings Citation Index–Social Science & Humanities (CPCI-SSH), using broad terms for enteric fever ("typhoid fever", "salmonella typhi", "enteric fever", "paratyphoid fever", "salmonella paratyphi"). The search was conducted in March, 2023, with no publication date restriction, and results were restricted to English-language systematic reviews. To prioritise the most relevant and recently published studies, we also searched Medline in July, 2024, using the same search terms for all studies published in English between Jan 1, 2020, to July 1, 2024. The contacts of authors were used to identity further key studies not identified in either search until Feb 28, 2025. Reference lists of included studies were hand-searched for further relevant studies.

SHOUT
SHARE
IT

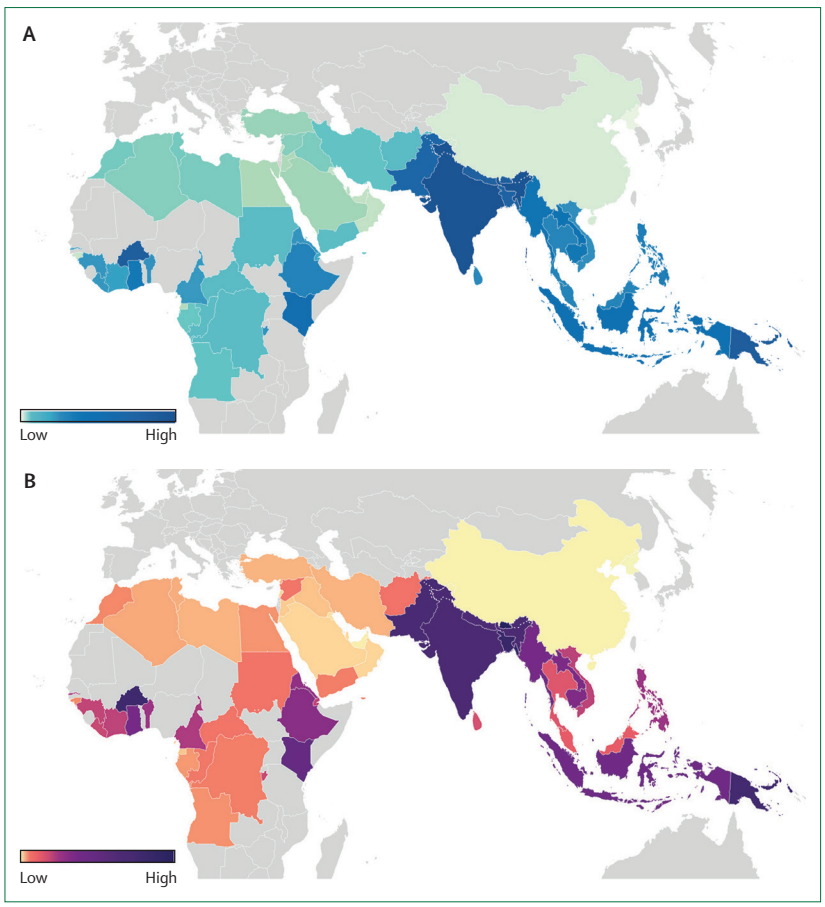

Figure 1: **Age-standardised incidence and mortality of enteric fever**
Age-standardised incidence (panel A) and mortality (panel B) of enteric fever in 75 endemic countries, per data from 2021. Reproduced from Piovani et al,[4] by permission of the authors.

Panel 1: **Terminology and definitions**

Definitions of drug resistance patterns

- Multidrug resistant: resistant to chloramphenicol, amoxycillin, and trimethoprim–sulphamethoxazole
- Fluoroquinolone non-susceptible: reduced susceptibility to ciprofloxacin (minimum inhibitory concentration >0·06 mg/L); resistance to nalidixic acid or pefloxacin is a marker
- Extensively drug resistant: resistant to chloramphenicol, amoxycillin, trimethoprim–sulphamethoxazole, ciprofloxacin, and ceftriaxone

WHO case definitions

- Acute typhoid fever: laboratory confirmation by culture or molecular methods of *Salmonella enterica* serotype Typhi (S Typhi) or detection of S Typhi DNA from a normally sterile site
- Relapse of typhoid fever: laboratory confirmation of S Typhi from a normally sterile site within 1 month of completing an appropriate course of antimicrobial treatment and resolution of symptoms
- Chronic typhoid carrier: evidence of shedding of S Typhi (positive stool culture or PCR) at least 12 months after finishing an appropriate course of antimicrobial treatment and the resolution of symptoms following a laboratory-confirmed episode of acute disease or two stool samples 12 months apart positive for S Typhi
- Convalescent carrier: evidence of shedding of S Typhi (positive stool culture or PCR) 1–12 months after finishing an appropriate course of antimicrobial treatment and the resolution of symptoms following a laboratory-confirmed episode of acute typhoid fever
- Suspected case of typhoid: fever for at least 3 out of 7 consecutive days in an endemic area or following travel from an endemic area, or fever for a least 3 out of 7 consecutive days within 28 days of being in household contact with a confirmed case of typhoid fever

inadequate hygiene and sanitation measures, or a long-cycle, in which there is contamination of the broader environment because of pollution of untreated water supplies by human faeces or when raw human faeces or untreated sewage is used as a crop fertiliser.[21]

The bacteria can survive in water and ice.[22] Contaminated fresh water, utensils, and food (including raw fruit and vegetables, food cooked at inadequate temperatures, unpasteurised dairy products, and shellfish harvested from contaminated water) can be sources of transmission.[22] Direct faecal–oral transmission and sexual transmission in men who have sex with men is reported.[23] Vertical transmission with neonatal typhoid is rare.[24]

Outbreaks of enteric fever in LMICs between 1990 and 2018 were mainly through waterborne transmission, which included faecal contamination from burst sewer pipes, lack of chlorination, unregulated water sources, and drinking water sources close to latrines.[25] In high-income countries outbreaks are more often foodborne and linked to food handlers, asymptomatic chronic carriers, or both.[26] The burden and importance of chronic carriers, defined as individuals with continued shedding of typhoidal bacteria in faeces or urine for more than a year after an acute infection (panel 1), as a source of infection in high burden areas has not been well studied.[21,27,28]

Disease pathophysiology

Human challenge studies suggest that bacteria passing through the gastric acid barrier after ingestion require an infectious dose between 10^3–10^4 bacteria for *S* Typhi and *S* Paratyphi A.[29,30] Evidence from other enteric infections suggests that reduced gastric acidity, due to gastrectomy or proton pump inhibitor treatment, could reduce the inoculum required.[31] Past infection with *Helicobacter pylori* is a further suggested risk factor.[32]

The bacteria pass through the wall of the ileum through M cells overlying the Peyers patches and are then ingested by monocyte-macrophage cells in the submucosa and mesenteric lymph nodes (figure 2).[33,34]

The bacteria survive intracellularly and travel via the lymphatic system and bloodstream to the reticuloendothelial system (liver, spleen, and bone marrow).[35] After multiplication in the reticuloendothelial system, re-invasion of the bloodstream coincides with the onset of symptoms.[33] The typical incubation period can vary according to the quantity of bacteria ingested but is typically 7–21 days, occasionally as short as 2 days, and with the majority of cases within 28 days.[36,37]

The median bacterial load in the bloodstream is only one bacteria per mL.[29,30,38,39] Children have higher blood bacterial counts than adults and the numbers for both decline with increasing duration of illness.[38] The bacterial load is ten times higher in the bone marrow.[39,40] About two-thirds of the bacteria in blood and bone marrow are intracellular.[38–40] The number of bacteria in the bone marrow correlates with the elevation in liver transaminases, and a higher proportion of bone marrow cultures are positive with increasing disease severity.[40,41] This correlation suggests that bacteria in the reticuloendothelial system reflect the in-host bacterial disease burden. Cytokines, such as TNF and IL-6, have been shown to be moderately elevated in blood but less so than seen in Gram-negative septic shock.[34] Specific host genetic polymorphisms, such as variation at *HLA-DRB1*, have been associated with risk of typhoid and severe disease.[42]

As the bacteria pass through the biliary system, gall bladder, and then back into the small intestine, in some patients the bacteria incite an inflammatory reaction at the sites of initial systemic entry in the terminal ileum. Ulceration, bleeding, and necrosis of the Peyer's patches can occur in Shwartzman and Koch type reactions.[43] This reaction can lead to gastrointestinal bleeding as well as intestinal perforation and peritonitis (figure 3A).

Short-term shedding of bacteria in the faeces can occur before and during acute infection and in the few weeks following clinical recovery.[21,29,30,44–46] Chronic carriage predominantly occurs in the context of gall bladder disease (panel 1, figure 3B) and rarely at other sites in the biliary system and urinary tract.[21,47–49] The bacteria form a dense bacterial biofilm on gallstones and other surfaces, occasionally also involving the intrahepatic bile ducts.[50] Chronic faecal carriage occurs in 2–5% of people after acute typhoid fever, is more common in females than males, and increases with age.[44] A quarter of asymptomatic carriers have no history of acute typhoid fever, and shedding in the faeces is sporadic.[44]

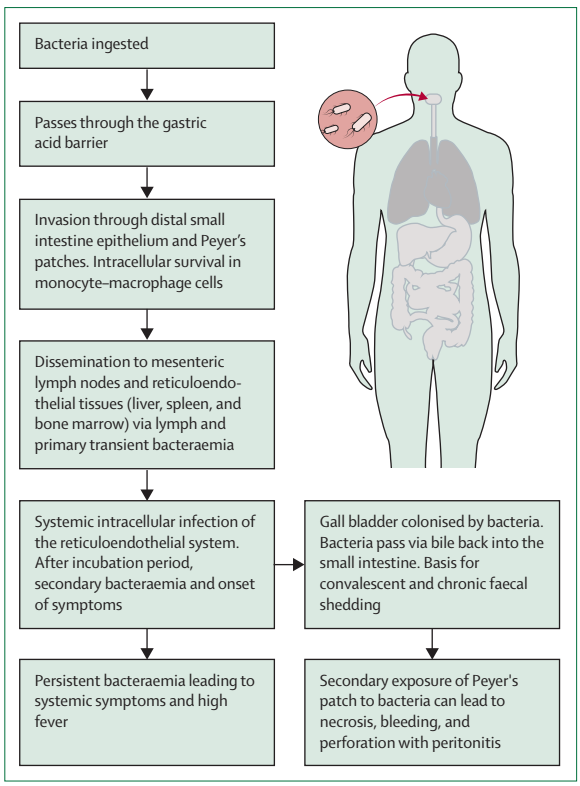
Bacteria ingested
Passes through the gastric acid barrier
Invasion through distal small intestine epithelium and Peyer's patches. Intracellular survival in monocyte–macrophage cells
Dissemination to mesenteric lymph nodes and reticuloendothelial tissues (liver, spleen, and bone marrow) via lymph and primary transient bacteraemia
Systemic intracellular infection of the reticuloendothelial system. After incubation period, secondary bacteraemia and onset of symptoms
Gall bladder colonised by bacteria. Bacteria pass via bile back into the small intestine. Basis for convalescent and chronic faecal shedding
Persistent bacteraemia leading to systemic symptoms and high fever
Secondary exposure of Peyer's patch to bacteria can lead to necrosis, bleeding, and perforation with peritonitis

Figure 2: **Stages in the pathophysiology of enteric fever**

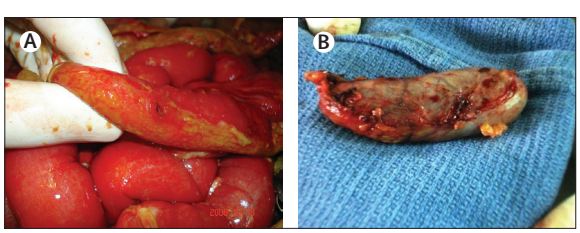

Figure 3: **Typhoid-related intestinal perforation and diseased gall bladder**
(A) A single perforation in the terminal ileum of a child in Viet Nam seen at laparotomy due to typhoid fever infection. (B) Diseased gall bladder removed from a Nepalese patient with chronic faecal carriage; *Salmonella enterica* serovar Typhi was isolated from the gall bladder contents.

Where in the world should enteric fever be considered as a differential diagnosis?

Most populations living in ecological conditions conducive to enteric fever transmission do not have population-based national surveillance systems and have poor access to diagnostic blood-culture facilities. In addition, there have been few high-quality primary incidence studies, as highlighted in a systematic review and meta-analysis of global typhoid fever incidence studies published between 1946 and 2018.[51] The review described high levels of disease in south and southeast Asia and some parts of sub-Saharan Africa. Since this review, further robust estimates have been derived from research studies conducted in affected regions using methodology that establish incidence by combining active blood culture surveillance with health utilisation surveys and adjustments for blood culture sensitivity.[52–56] Incidence rates exceeding 100 per 100 000 person-years is a threshold used to define settings as high burden for enteric fever.[21]

Prospective population-based studies between 2016 and 2019 reported the adjusted incidence of typhoid fever per 100 000 person-years: Garrett and colleagues[52] reported 913 in Dhaka, Bangladesh, 330 in Kathmandu, Nepal, and 103 in Karachi, Pakistan; and Meiring and

colleagues[53] reported 1135 in Dhaka, Bangladesh, 1062 in Kathmandu, Nepal, and 176 in Karachi, Pakistan. The adjusted incidence rates for paratyphoid per 100 000 person-years were 128 and 42 in Bangladesh, 46 and 6 in Nepal, and 23 and 1 in Pakistan. The highest incidence of disease was in children aged 2–4 years in Bangladesh and Pakistan but cases in children younger than 2 years were also reported. In Nepal, the highest incidence was among individuals aged 5–25 years. A prospective study conducted in children at three urban sites and one rural site in India between 2017 and 2020 gave estimated typhoid fever incidences ranging from 12 to 1622 per 100 000 child-years between the ages of 6 months and 14 years and from 108 to 970 per 100 000 person-years in those aged 15 years or older.[54] The overall incidence of paratyphoid was 68 per 100 000 child-years.

Surveillance studies conducted in 12 African countries have shown a wider variation of typhoid fever incidence compared with south Asia.[53,55–57] Incidences above 100 per 100 000 person-year observations have been documented in sites in Burkina Faso, Ghana, Madagascar, Tanzania, Kenya, Democratic Republic of Congo, Nigeria, and Malawi, with lower levels in other countries.[53,55–57]

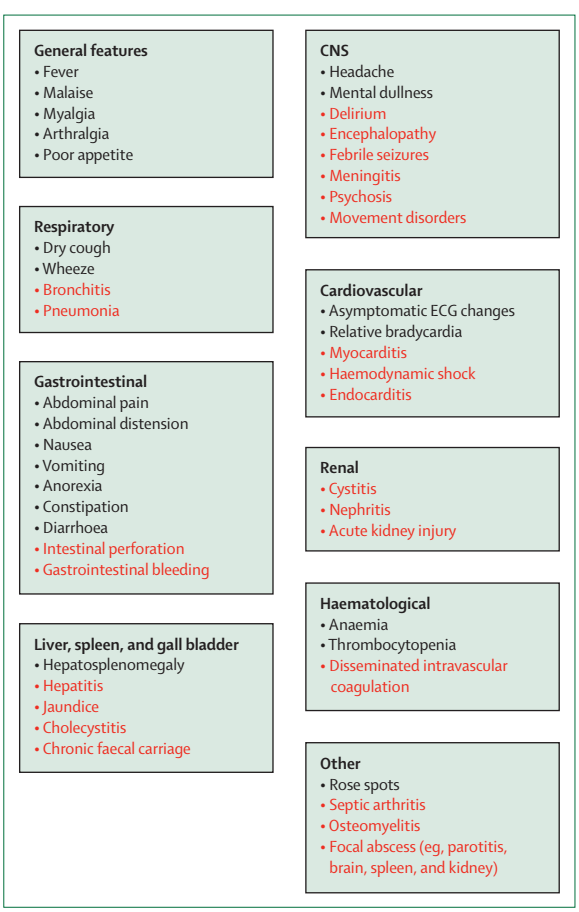

Figure 4: **Signs, symptoms, and complications in enteric fever**
Common signs and symptoms in black, complications in red. ECG=electrocardiogram.

Similar data on incidence rates from other regions in the world are generally lacking. Some countries within Oceania have reported high incidence levels.[4,58] Data from Latin America are also sparse, but suggest the incidence is low.[4,28]

Overall, these studies have shown an appreciable burden of enteric fever in children younger than 15 years, with high levels in urban and some rural areas. The burden of enteric fever is dynamic as WASH interventions and vaccination can lead to reductions in transmission while evolving patterns of increasing antimicrobial resistance can increase incidence in different settings over time.[10,20] Incidence patterns will continue to evolve with the potential effects of climate change, population growth, extreme weather events, and urbanisation.[59]

How does enteric fever present?

In the classic descriptions of enteric fever, the illness begins with a gradual onset of fever over 3–7 consecutive days, a step ladder of increasingly high temperature spikes, with general malaise, headache, a dry cough, and myalgia (figure 4).[60–62] Occasionally the disease presents with a more acute onset but without the paroxysms and chills seen in malaria. Untreated enteric fever progresses in the second week of illness with a high persistent fever, sometimes with a relative bradycardia, a palpable liver or spleen and with increasing mental dullness and confusion. If left untreated, in the second and third week complications develop.[60–62] This classic progression is more rarely seen now as patients generally present early to medical care, after a few days of fever, and have frequently already taken antimicrobial therapy from a shop or pharmacy before attending a health-care provider.

In recent descriptions in children, common clinical features are consecutive days of high-grade fever (39–40°C), nausea, vomiting, diarrhoea, constipation, hepatomegaly, splenomegaly, and abdominal distension.[63,64] Anaemia and leukopenia are common laboratory findings. Young, pre-school age children can present with a non-specific fever without localising signs and inconclusive laboratory results, or alternatively with toxicity and atypical clinical features.[63,64]

In adults, gastrointestinal symptoms (abdominal pain, nausea, vomiting, diarrhoea, or constipation) with over three consecutive days of slowly rising fever raise the suspicion of enteric fever.[63,65] Headache, anorexia, hepatosplenomegaly, and cough can occur. Rose spots are blanching, erythematous, maculopapular lesions, 2–4 mm in diameter that usually occur on the trunk; when present they are transient, difficult to see on darker skin tones, and in recent reviews reported in less than 10% of cases.[63] They are not pathognomonic for enteric fever. Occasionally, young children and adults can have a short febrile illness with a transient bacteraemia with none of the typical features of typhoid fever.[21,29,30,66] Paratyphoid fever has been found to be clinically indistinguishable

from typhoid in some studies but described as a milder disease in others.[65,67] A patient story is described in panel 2.

Possible complications

Complications generally develop in untreated disease in the second or third week of illness following late presentation to medical care or the delayed initiation of appropriate antimicrobial treatment (figure 4).[62,68] Multidrug-resistant (MDR; ie, resistant to ampicillin, chloramphenicol, and co-trimoxazole),[69] fluoroquinolone non-susceptible (FQNS),[70] and extensively drug resistant (XDR; ie, MDR, FQNS, and ceftriaxone-resistant)[71] infections have been implicated as risk factors for complications (panel 1). A high bacterial inoculum could also be a risk factor for complications.[38] There is no strong evidence to suggest an association between HIV and enteric fever occurrence and/or severity, unlike with the non-typhoidal *Salmonella*.[72] Recent case–fatality ratio (CFR) estimates are in the range of 0·3–6·7% overall,[70,73–75] 4·45% in hospitalised cases,[74] and up to 15·5% in cases with typhoid intestinal perforation.[73]

Typhoid intestinal perforation is a life-threatening complication (figure 3A). In studies in Africa, one in five patients with typhoid intestinal perforation died.[76] Lack of prompt access to surgical resources, intensive care, and postoperative care could contribute to these deaths.[76–79] Common postoperative complications include surgical site infection, wound dehiscence, and enterocutaneous fistula, all of which increase length of hospital stay and place substantial economic burden on families.[78–80]

The syndrome of encephalopathy is also associated with high mortality.[81–83] An abnormal affect with mental dullness can occur.[11,61–65] In some patients, mental dullness can progress to delirium, abnormal movements, obtundation, and coma accompanied by toxicity, evidence of myocarditis, and haemodynamic shock.[81–83] The pathogenesis of the syndrome is not well established.

Many other complications occur in enteric fever (figure 4). Gastrointestinal bleeding is relatively common, but is rarely life threatening. Hepatitis, cholecystitis, acalculous cholecystitis, pneumonia, and anaemia are also common complications in some case series.[60-64,68–71] Rare complications include septic arthritis and osteomyelitis, extra-intestinal abscesses, meningitis and brain abscess in the very young, splenic infarcts and rupture, spontaneous primary pneumothorax, catatonia, psychosis, and sensorineural hearing loss.[60–64,68–71] Recurrence of the illness with the same symptoms and signs can occur within 2–4 weeks of apparent recovery. This recurrence is usually a relapse of the original infection, but occasionally can be a re-infection, and this can be distinguished by molecular typing.[84]

What diagnostic tests are available?

Making a confident diagnosis of enteric fever based on clinical features alone is challenging. Non-specific signs and symptoms overlap with those of other common febrile illnesses. Malaria is an important differential but can be excluded with a blood smear or malaria rapid diagnostic test (RDT). Other important differential diagnoses include flavivirus illness (eg, dengue, chikungunya, or Zika), rickettsia infections (eg, scrub and murine typhus), leptospirosis, brucella, and other acute viral infections (eg, influenza, acute hepatotropic viruses).[11,65] RDTs are available to help with the diagnosis of some of these infections in resource-poor settings.[85] Attempts to develop a clinical diagnostic score for enteric fever have not been successful.[65]

Simple laboratory tests could help. The total white cell count is usually within, or just below, the normal range in enteric fever.[60–65] Leucocytosis (raised white cell count) could point toward intestinal perforation or an occult pyogenic infection, or leptospirosis or scrub typhus. A mild normochromic or hypochromic anaemia, mild thrombocytopenia, and mild elevation of liver transaminases with a normal bilirubin are common. C-reactive protein is also usually elevated.

Blood culture is the pragmatic reference standard test, but has a sensitivity that varies in different reports from 40% to 80% and might not be available where enteric fever is common.[86,87] In a systematic review of studies comparing blood culture with bone marrow culture, sensitivity of blood culture was 66% when

Panel 2: Clinical case

A male health-care worker in India, aged 34 years and previously well, presented to a hospital in south India with 5 days of fever up to 39°C, rigors, myalgia, and anorexia. There was no history of abdominal pain, nausea, vomiting, diarrhoea, cough, dyspnoea, altered sensorium, seizure, or focal neurological deficits. He had no recent travel and had not consumed street food. His temperature on admission was 37·7°C, pulse 110 beats per minute, blood pressure 110/80 mm Hg, respiratory rate 20 breaths per minute, and Glasgow Coma Scale score of 15. Systems examination was normal, with the exception of a coated tongue. The patient was admitted, started on empirical treatment with 1 g of azithromycin once daily and intravenous paracetamol. His laboratory testing reported C-reactive protein of 92·5 mg/L (normal range <5 mg/L) and normal complete blood count, liver transaminases, urea, and creatinine. Rapid diagnostic tests for scrub typhus, malaria, microfilariae, and dengue were negative. A chest x-ray and abdominal pelvic ultrasound were normal. His blood culture was positive after 14 h with a Gram-negative bacillus seen on microscopy; the isolate was subsequently confirmed to be *Salmonella enterica* serovar Typhi, susceptible to azithromycin and ceftriaxone and resistant to ciprofloxacin. The patient continued with azithromycin and remained febrile until day 4 of admission. Azithromycin was continued for a total of 7 days, at which point the patient was discharged having made a full recovery.

compared with bone marrow culture results.[86] The low numbers of *S* Typhi present in blood and the frequency of previous antimicrobial treatment are key reasons for the low sensitivity of blood culture;[38,87] a large volume of blood in the blood culture should increase the culture yield.[88] The estimated sensitivity of bone marrow aspirate is greater than 90%, and it can remain positive for several days even after starting effective antimicrobials.[39,40,86,89] This high yield of bone marrow aspirate culture reflects the higher bacterial load in the reticuloendothelial system than in blood.[39] Although bone marrow aspiration is technically challenging and more invasive than a blood culture, it can be valuable as a second-line investigation in patients with prolonged fever and a negative blood culture to help distinguish from differentials such as brucellosis or tuberculosis. The presence of typhoidal *Salmonella* in stool or urine could indicate acute enteric fever, but could also represent chronic carriage with a different reason for the fever.[88]

The detection of specific DNA sequences of the *S* Typhi or *S* Paratyphi genome in clinical samples is a further diagnostic option.[35,90,91] The relatively low amount of bacterial DNA found in human blood makes detection challenging. The expense and technical challenges of molecular diagnostics in laboratories in an endemic setting are an additional barrier.

The Widal test is still widely used in LMICs because it is cheap and simple to perform, although it lacks standardisation of reagents and validated cut-offs for diagnosis of an acute enteric fever.[88] The Widal test detects agglutinating antibodies against *S* Typhi and *S* Paratyphi lipopolysaccharide (O) antigens and flagellar (H) antigens.[88] False-positive results, due to past infection or cross-reacting antibodies with other Enterobacteriaceae, or false-negative results due to low levels of antibody, are common.[61] Paired acute and convalescent serum samples can show a rising antibody titre or seroconversion, but in practice decisions are made on the basis of a single acute sample, which can often be misleading. The lack of diagnostic accuracy means the Widal test cannot be recommended as a reliable diagnostic option.

Commercially available RDTs are also widely used, although many have not undergone formal diagnostic accuracy evaluation. Of those that have been evaluated, such as Typhidot-M (Reszon Diagnostics International, Malaysia), TUBEX-TF (IDL Diagnostics, Sweden), Test-it Typhoid IgM (Life Assay Diagnostics, South Africa), and Enterocheck WB (Tulip Diagnostics, India), although an improvement over the Widal test, the diagnostic accuracy is not sufficient for these tests to be recommended.[92–94] However, in reality, in many LMICs a Widal test or an RDT are the only diagnostic tests available.

Other diagnostic tests are in development. The typhoid/paratyphoid diagnostic assay detects *S* Typhi and *S* Paratyphi A IgA antibody secreted by isolated T cells, and performed well in studies conducted in south Asia.[94] Encouraging data on IgA serology responses against the HylE antigens have been found in studies in Nigeria and Bangladesh.[95–97] Other research approaches include studying host gene signatures[98] and diagnostic plasma metabolites.[99] Vi serology has been used to identify chronic faecal carriers in outbreak settings but performs poorly in endemic areas.[100,101] New immunogenic antigens and metabolite biomarkers for the detection of chronic carriage are being explored.[102,103]

Treatment

Patients with enteric fever require treatment with an antimicrobial agent, supportive care, and the management of complications.[11,61,62,104,105] In LMIC settings, patients are usually treated empirically in the first week of illness with an oral antimicrobial as part of outpatient management,

	First-line treatment	Alternative treatment
Uncomplicated enteric fever		
Unknown susceptibility	Azithromycin, 20 mg/kg per day, 7–10 days	..
Fully susceptible	Ciprofloxacin, 20 mg/kg per day, 7–10 days	Chloramphenicol*, 50–75 mg/kg per day, 14–21 days; amoxicillin, 75–100 mg/kg per day, 14–21 days; trimethoprim–sulphamethoxazole†, 8–40 mg/kg per day‡, 14–21 days; cefixime, 20 mg/kg per day, 7–14 days; ofloxacin 10–15 mg/kg per day, 7–10 days; levofloxacin 10–15 mg/kg per day, 7–10 days
Multidrug resistant§	Ciprofloxacin, 20 mg/kg per day, 7–10 days	Cefixime, 20 mg/kg per day, 7–14 days; azithromycin, 20 mg/kg per day, 7–10 days; ofloxacin 10–15 mg/kg per day, 7–10 days; levofloxacin 10–15 mg/kg per day, 7–10 days
Fluoroquinolone non-susceptible¶	Azithromycin, 20 mg/kg per day, 7–10 days	..
Extensively drug resistant||	Azithromycin, 20 mg/kg per day, 7–10 days	..
Severe enteric fever requiring parenteral treatment†††**		
Unknown susceptibility	Ceftriaxone, 50–75 mg/kg per day, 10–14 days	..
Fully susceptible	Ciprofloxacin‡‡, 20 mg/kg per day, 10–14 days	Ceftriaxone, 50–75 mg/kg per day, 10–14 days
Multidrug resistant§	Ciprofloxacin‡‡, 20 mg/kg per day, 10–14 days	Ceftriaxone, 50–75 mg/kg per day, 10–14 days
Fluoroquinolone non-susceptible¶	Ceftriaxone, 50–75 mg/kg per day, 10–14 days	Azithromycin§§, 20 mg/kg per day, 10–14 days
Extensively drug resistant||	Meropenem, 60 mg/kg per day, 10–14 days	Azithromycin§§, 20 mg/kg per day, 10–14 days

Culture and susceptibility result often unavailable; empirical treatment should be based on regional knowledge of susceptibility patterns.[11,104,105,107–109] *Can cause bone marrow suppression, oral route preferred. †Inexpensive, can cause allergic reactions and nephrotoxicity, not suitable during pregnancy or for children younger than 2 years. ‡8 mg/kg trimethoprim and 40 mg/kg sulphamethoxazole. §Resistant to chloramphenicol, amoxycillin, trimethoprim–sulphamethoxazole. ¶Non-susceptible to ciprofloxacin (nalidixic acid or pefloxacin resistant or ciprofloxacin resistant by disk testing). ||Resistant to chloramphenicol, amoxycillin, trimethoprim-sulphamethoxazole, ciprofloxacin, and ceftriaxone. **In intestinal perforation, antimicrobial therapy should cover other aerobic and anaerobic gastrointestinal bacteria. ††In severe typhoid (characterised by delirium, obtundation, coma, or shock) dexamethasone can be beneficial; one 3 mg/kg dose dexamethasone infused intravenously over 30 min, followed by eight doses of 1 mg/kg every 6 h. ‡‡Ofloxacin and levofloxacin are effective alternatives. §§Consider combining meropenem with azithromycin.

Table 1: **Antimicrobial treatment options for enteric (typhoid and paratyphoid) fever**

and most recover within a week.[61] Hospital admission is required for patients with persistent vomiting who are unable to tolerate fluids and oral medications, with signs of severe dehydration or unstable vital signs and clinician concern of toxicity. Further indications for hospital admission include features of severe or complicated disease, signs of severe disease as per the Integrated Management of Childhood Illness, or where the diagnosis is uncertain.[11] Patients might decline hospital admission due to various factors, including treatment costs. Returning travellers are usually admitted to hospital until stable, although outpatient management can be a suitable alternative in the absence of complications.[106]

Antimicrobials used for treating enteric fever have included chloramphenicol, amoxicillin, trimethoprim–sulphamethoxazole, fluoroquinolones (eg, ciprofloxacin, ofloxacin, and levofloxacin), azithromycin, and cephalosporins (eg, ceftriaxone and cefixime). Systematic reviews of the comparative efficacy of antimicrobials in enteric fever treatment have been unable to draw firm conclusions on the presence or absence of important differences when the infecting isolate is susceptible to that agent. In addition, many of the individual randomised controlled trials have methodological weaknesses.[107–109]

The choice of antimicrobial depends on local or national guidelines, ideally informed by epidemiological data of local antimicrobial resistance patterns (table 1).[11,104,105,110–116] Common resistance patterns vary by location and over time.[10,20] WHO guidelines recommend that ciprofloxacin, ceftriaxone, and azithromycin should be considered first-choice treatments.[104] Treatment durations of 7–14 days or >5 days after fever resolution have traditionally been recommended. Shorter courses of treatment might be effective in uncomplicated disease and could be useful in outbreak situations in LMICs.[107,109]

Ciprofloxacin is not a suitable choice in much of south Asia and some areas of sub-Saharan Africa because of widespread low-level resistance (indicated by resistance to nalidixic acid or pefloxacin) and localised high-level resistance.[10,20,115] Azithromycin is currently an effective option. There are scattered reports of in-vitro azithromycin resistance based on a minimum inhibitory concentration breakpoint for susceptibility of ≤16 mg/L.[116–118] Of note, the clinical response to azithromycin when the in-vitro minimum inhibitory concentrations of the infecting isolate is >16 mg/L is yet to be fully defined. For children, patients admitted to hospital, and when resistance to other drugs is uncertain, parenteral ceftriaxone has been a safe option. Since 2017 there has been a large and ongoing outbreak of XDR typhoid in Pakistan.[119,120] For XDR typhoid, meropenem can be used in severe illness and azithromycin can be used in the outpatient setting.[114,121] The cephalosporin resistance in XDR strains is mediated by carriage of a plasmid-mediated $bla_{CTX\text{-}M\text{-}15}$ extended spectrum β-lactamase gene.[120] These infections have also been seen in other countries in travellers from Pakistan.[114] There are sporadic reports of other patterns of extended-spectrum cephalosporin resistance and carbapenem resistance in India and elsewhere.[122–125] Although paratyphoid fever has remained susceptible to most antimicrobials except ciprofloxacin, at the point of presentation paratyphoid cannot be differentiated from typhoid.[67,126]

Antimicrobial adjustments are warranted if antimicrobial resistance from organisms isolated in culture is reported or if clinical symptoms do not improve after 5 days of appropriate antimicrobial therapy. Typical defervescence time ranges from 5 days to 7 days when patients are on an effective antimicrobial, and patients often feel better before their temperature returns to normal.[11,61,62] Persistent fever in the absence of other signs of complications with otherwise general clinical improvement is not a marker of treatment failure. De-escalation of intravenous to oral antimicrobials should be considered on the basis of susceptibility results. If a blood culture shows no growth or is unavailable, and clinical suspicion is strong, a therapeutic trial with an appropriate antimicrobial based on local resistance patterns is appropriate. In areas where infections such as scrub or murine typhus and leptospirosis are common and can mimic enteric fever, the addition of empirical doxycycline should be considered.

Whether there is added benefit of using combinations of antimicrobials in enteric fever, compared with the efficacy of each drug on its own, is unclear. Combining the high intracellular concentrations of azithromycin with the extracellular activity of a β-lactam antimicrobial has been suggested to be useful in small, uncontrolled clinical trials.[127] An ongoing clinical trial is examining the efficacy of an azithromycin and cefixime combination in suspected cases of enteric fever in south Asia.[128] Other antimicrobials could be needed if resistance to all current options emerges.[129]

Management of complications

Patients who develop complications require additional supportive treatments, including full intensive care support, blood transfusion for a gastrointestinal haemorrhage, and surgery if there is an intestinal perforation and peritonitis.[78,79,130] Antimicrobial choice could need to be broadened in the event of a perforation causing a peritonitis; however, other complications generally resolve with effective antimicrobial therapy. Relapse rates vary between 2% and 10% but depend on the antimicrobial treatment given and the resistance pattern of the infecting organism.[107–109] Relapse usually responds to a further course of the same antimicrobial used for the primary episode.[11,61,62]

In severe typhoid characterised by altered consciousness and haemodynamic shock, a randomised controlled trial (RCT) in Indonesia found that high doses of dexamethasone (3 mg/kg followed by 1 mg/kg every 6 h for a total of 48 h) reduced mortality in patients treated

	Mechanism and type	Dose and route	Eligible persons	Protective efficacy*
Ty21a	Live attenuated, Ty2 strain of *S* Typhi	3 or 4 oral doses on alternate days†	Age ≥6 years; immunocompetent non-pregnant	43% (30–55) at 1–5 years‡
Vi-PS	Purified Vi capsular polysaccharide of Ty2 *S* Typhi strain	Single injection	Age ≥2 years	58% (44–69) at 1–3 years‡
TCV (Vi-TT)	Subunit, Vi capsular polysaccharide linked to tetanus toxoid	Single injection	Age 6 months to 65 years	83% (77–88) at 1–2 years§; 78% (66–86) at 4 years¶; 54% (13–76) at 3–5 years‖
TCV (Vi-DT)	Subunit Vi capsular polysaccharide linked to diphtheria toxoid	Single injection	Age 6 months to 45 years	Pre-approval based on immunogenicity data**
TCV (Vi-CRM_{197})	Subunit Vi capsular polysaccharide linked to CRM_{197}	Single injection	Age 6 months to 45 years	Pre-approval based on immunogenicity data**

S Typhi=*Salmonella enterica* serotype Typhi. *Data are percentage (95% CI). †Canada and the USA recommend a 4-capsule course. ‡Systematic review and meta-analysis, calculated as: (1 – risk ratio) × 100%.[5] §Randomised controlled trials and adjusted cluster randomised controlled trial, calculated as: (1 – incidence rate ratio) ×100%.[5] ¶Randomised controlled trial in children in Malawi.[139] ||Extrapolated medium-term efficacy from a cluster randomised controlled trial in Bangladesh.[140] **WHO prequalified vaccines.[135]

Table 2: **Current prequalified vaccines for typhoid fever**

with chloramphenicol.[81] Methodological issues make it difficult to draw definitive conclusions from this study and further trials on the utility of steroids in encephalopathy and shock are needed.[131]

Chronic faecal carriers can be a source of infection to others in the community. A systematic review of studies of the antimicrobial treatment of chronic carriage identified eight studies but only one RCT.[132] Fluoroquinolones are effective in eradicating chronic carriage of susceptible isolates after a 28-day course. Results of the only double-blind RCT showed an eradication rate of 92% in those given a 28-day course of norfloxacin compared with 11% in those given placebo. Six studies evaluated ampicillin or amoxycillin in a 4–6-week course with cure rates around 70%. Cholecystectomy could be an option but should be balanced with the risk of surgical complications (figure 2B). These studies pre-date the emergence of widespread drug resistance and further clinical trials in this area, for example using azithromycin, would help guide modern management.

Prevention of enteric fever

Enteric fever can be prevented through wider access to safe drinking water, improved WASH infrastructure, education on food hygiene practices, public health disease surveillance systems (including identification, treatment, and contract tracing of chronic carriers), and vaccination.[6,26,133,134] Safe water sources and point-of-use interventions for untreated water (including chlorination or solar disinfection) have been proven to be highly effective in preventing transmission of faecal–oral pathogens.[135] WASH interventions carry the potential to have the greatest impact in regions of high disease burden.

WHO has approved a live oral attenuated vaccine (Ty21a), a Vi polysaccharide and, more recently, has prequalified three types of typhoid conjugate vaccine (TCVs) for the prevention of typhoid fever (table 2).[136,137] Other TCVs have been licensed by national regulatory authorities. The level of protection with TCVs has been shown to be high compared with the previous approved vaccines, and in 2018 WHO recommended the use of single-dose TCV in high-burden typhoid areas and areas with high rates of antimicrobial resistance.[133]

The Ty21a vaccine is approved for individuals aged 6 years and older and is an oral capsule. In a recent systematic review and meta-analysis, the random effects pooled efficacy was 43% (95% CI 30–53) at 1–5 years post-vaccination.[5] Recommendations for a three dose or four dose schedule vary between countries and comparative efficacy of these varying dosing schedules is lacking. Rare side-effects include fever, nausea, or vomiting.[136] Ty21a vaccines might not be reliably accessible in endemic regions, including Bangladesh, India, and Pakistan. Purified capsular-polysaccharide-based vaccines are available as a single intramuscular injection for individuals aged 2 years and older, providing up to 3 years of protection. The random effects pooled efficacy 1–3 years post vaccination was 58% (44–69).[5] Side-effects are rare but include fever or local reactions at the injection site.[136] Although these older vaccines are widely used for preventing typhoid in travellers to endemic areas, they have not found a place in public health programmes in high burden settings.

TCVs have been developed to provide better and durable immune protection against typhoid in endemic settings.[133] TCVs are based on Vi-polysaccharide conjugated to carrier proteins such as tetanus toxoid (Vi-TT), CRM_{197}, diphtheria toxoid, or recombinant *Pseudomonas aeruginosa* exotoxin A. A systematic review estimated the pooled efficacy of a single dose of TCV (Vi-TT) to be 83% (95% CI 77–88) at 1–2 years post-immunisation based on data from studies conducted in Bangladesh, India, Malawi, and Nepal including more than 100 000 participants aged 6 months to 16 years.[5,138–140] The effectiveness of TCV was lower in children aged 5 years and younger (73% [53–85]) compared with children older than 5 years (87% [80–91]).[5] Follow-up data showed high protection after 4 years in a cohort from Malawi (78% [66–86]).[141] A decline in vaccine effectiveness was observed after 3–5 years, dropping as low as 54% (13–76) in a cohort in Bangladesh.[142] Given that antibody titres were lower in children aged younger than 2 years, a booster vaccination could be beneficial in this age group, but this question is yet to be resolved.[143] Side-effects such as fever, local swelling, and seizures occurred rarely with TCVs in children and adults. Children younger than 5 years were mainly affected by febrile seizures, as they are in the general population. No long-term sequelae have been reported.[144]

To date, WHO lists three types of TCV as prequalified vaccines and recommends the use of single-dose TCV in high-burden typhoid areas and areas with high rates of antimicrobial resistance.[133,137] Several countries, including Bangladesh, Burkina Faso, India, Kenya, Liberia, Malawi, Nepal, Pakistan, Samoa, and Zimbabwe, have introduced TCV in routine vaccination programmes and additional mass vaccination campaigns were conducted in Tuvalu and Fiji.[6,145] The introduction of TCVs in the routine immunisation programmes in LMICs is a crucial step toward the control of this important disease.[6] Although these vaccines are not yet universally licensed, their demonstrated advantages over earlier vaccines suggest that recommendations for travellers to endemic areas are likely to be updated in the future.

The absence of licensed vaccines to prevent paratyphoid fever is a gap, although studies of potential vaccines are in progress.[146] Challenges in disease surveillance, diagnostics, and vaccine efficacy in endemic areas reinforce the need to implement WASH interventions.

Conclusions

Case management of enteric fever remains challenging. Current diagnostic tests for acute enteric fever do not have the diagnostic accuracy to be reliably used at the point of care, resulting in overuse of antimicrobials and empiric treatment.[8] A cheap, reliable, and accurate enteric fever diagnostic would provide a step change in treatment and disease control.[147] There is a looming threat of further antimicrobial resistance, and steps to prepare with data on the efficacy of alternative antimicrobials for treatment are needed.[9,10,129] Effective antimicrobial treatments are needed that cure symptoms but also stop shedding of bacteria in faeces that drives onward transmission.[21] Considering the high level of adaptation of these bacteria to a narrow niche, with humans the only natural host and reservoir,[33] the deployment of typhoid conjugate vaccines, strengthening of WASH infrastructure, development of accurate point of care diagnostics, provision of effective antimicrobial regimens, and novel approaches to the detection and treatment of chronic carriers, could make the elimination of enteric fever an achievable goal.[148]

Contributors

RK and CMP performed all literature searches. All authors contributed to drafting the manuscript. All authors critically reviewed and approved the final version of the manuscript.

Declaration of interests

AK, FNQ, and CMP are involved in the ACT-South Asia trial, which is funded by a Joint Global Health Trials Scheme (MR/TOO5033/1) award to the University of Oxford. RK is involved in the Research, Evidence and Development Initiative (READ-It; project number 300342-104), which is funded by the UK government. All other authors declare no competing interests.

Acknowledgements

We thank the patients who allowed us to use the photos of the intestinal perforation and diseased gall bladder and the patient who allowed us to share the story of their clinical illness.

Editorial note: The Lancet Group takes a neutral position with respect to territorial claims in published maps and text.

References

1 Meiring JE, Khanam F, Basnyat B, et al. Typhoid fever. *Nat Rev Dis Primers* 2023; **9:** 71.
2 Marchello CS, Dale AP, Pisharody S, Rubach MP, Crump JA. A systematic review and meta-analysis of the prevalence of community-onset bloodstream infections among hospitalized patients in Africa and Asia. *Antimicrob Agents Chemother* 2019; **64:** e01974–2019.
3 Debellut F, Friedrich A, Baral R, Pecenka C, Mugisha E, Neuzil KM. The cost of typhoid illness in low- and middle-income countries, a scoping review of the literature. *PLoS One* 2024; **19:** e0305692.
4 Piovani D, Figlioli G, Nikolopoulos GK, Bonovas S. The global burden of enteric fever, 2017–2021: a systematic analysis from the global burden of disease study 2021. *EClinicalMedicine* 2024; **77:** 102883.
5 Batool R, Qamar ZH, Salam RA, Yousafzai MT, Ashorn P, Qamar FN. Efficacy of typhoid vaccines against culture-confirmed *Salmonella* Typhi in typhoid endemic countries: a systematic review and meta-analysis. *Lancet Glob Health* 2024; **12:** e589–98.
6 Hancuh M, Walldorf J, Minta AA, et al. Typhoid fever surveillance, incidence estimates, and progress toward typhoid conjugate vaccine introduction—worldwide, 2018–2022. *MMWR Morb Mortal Wkly Rep* 2023; **72:** 171–76.
7 Buss I, Genton B, D'Acremont V. Aetiology of fever in returning travellers and migrants: a systematic review and meta-analysis. *J Travel Med* 2020; **27:** taaa207.
8 Sapkota J, Roberts T, Basnyat B, Baker S, Hampton LM, Dittrich S. Diagnostics for typhoid fever: current perspectives and future outlooks for product development and access. *Open Forum Infect Dis* 2023; **10** (suppl 1)**:** S17–20.
9 Browne AJ, Kashef Hamadani BH, Kumaran EAP, et al. Drug-resistant enteric fever worldwide, 1990 to 2018: a systematic review and meta-analysis. *BMC Med* 2020; **18:** 1.
10 Browne AJ, Chipeta MG, Fell FJ, et al, and the GRAM Typhoid Collaborators. Estimating the subnational prevalence of antimicrobial resistant *Salmonella enterica* serovars Typhi and Paratyphi A infections in 75 endemic countries, 1990–2019: a modelling study. *Lancet Glob Health* 2024; **12:** e406–18.
11 Basnyat B, Qamar FN, Rupali P, Ahmed T, Parry CM. Enteric fever. *BMJ* 2021; **372:** n437.
12 Parkhill J, Dougan G, James KD, et al. Complete genome sequence of a multiple drug resistant *Salmonella enterica* serovar Typhi CT18. *Nature* 2001; **413:** 848–52.
13 Johnson R, Mylona E, Frankel G. Typhoidal Salmonella: distinctive virulence factors and pathogenesis. *Cell Microbiol* 2018; **20:** e12939.
14 Song J, Gao X, Galán JE. Structure and function of the *Salmonella* Typhi chimaeric $A(_2)B(_5)$ typhoid toxin. *Nature* 2013; **499:** 350–54.
15 Gibani MM, Jones E, Barton A, et al. Investigation of the role of typhoid toxin in acute typhoid fever in a human challenge model. *Nat Med* 2019; **25:** 1082–88.
16 McClelland M, Sanderson KE, Clifton SW, et al. Comparison of genome degradation in Paratyphi A and Typhi, human-restricted serovars of *Salmonella enterica* that cause typhoid. *Nat Genet* 2004; **36:** 1268–74.
17 Wong VK, Baker S, Pickard DJ, et al. Phylogeographical analysis of the dominant multidrug-resistant H58 clade of *Salmonella* Typhi identifies inter- and intracontinental transmission events. *Nat Genet* 2015; **47:** 632–39.
18 da Silva KE, Tanmoy AM, Pragasam AK, et al. The international and intercontinental spread and expansion of antimicrobial-resistant *Salmonella* Typhi: a genomic epidemiology study. *Lancet Microbe* 2022; **3:** e567–77.
19 Tanmoy AM, Hooda Y, Sajib MSI, et al. Paratype: a genotyping tool for *Salmonella* Paratyphi A reveals its global genomic diversity. *Nat Commun* 2022; **13:** 7912.
20 Carey ME, Dyson ZA, Ingle DJ, et al, and the Global Typhoid Genomics Consortium Group Authorship. Global diversity and antimicrobial resistance of typhoid fever pathogens: insights from a meta-analysis of 13,000 *Salmonella* Typhi genomes. *eLife* 2023; **12:** e85867.
21 Crump JA. Progress in typhoid fever epidemiology. *Clin Infect Dis* 2019; **68** (suppl 1)**:** S4–9.

22 Mitscherlich E, Marth H. Special part bacteria considered in alphabetical order: vide index. In: Mitscherlich E, Marth EH, eds. Microbial survival in the environment. Springer, 1984: 1–560.

23 Reller ME, Olsen SJ, Kressel AB, et al. Sexual transmission of typhoid fever: a multistate outbreak among men who have sex with men. *Clin Infect Dis* 2003; **37:** 141–44.

24 Reed RP, Klugman KP. Neonatal typhoid fever. *Pediatr Infect Dis J* 1994; **13:** 774–77.

25 Appiah GD, Chung A, Bentsi-Enchill AD, et al. Typhoid outbreaks, 1989–2018: implications for prevention and control. *Am J Trop Med Hyg* 2020; **102:** 1296–305.

26 Brockett S, Wolfe MK, Hamot A, Appiah GD, Mintz ED, Lantagne D. Associations among water, sanitation, and hygiene, and food exposures and typhoid fever in case-control studies: a systematic review and meta-analysis. *Am J Trop Med Hyg* 2020; **103:** 1020–31.

27 WHO. Typhoid: Vaccine Preventable Diseases Surveillance Standards. Sept 4, 2018. https://www.who.int/publications/m/item/vaccine-preventable-diseases-surveillance-standards-typhoid (accessed July 11, 2025).

28 Lagos RM, Sikorski MJ, Hormazabal JC, et al. Detecting residual chronic *Salmonella* Typhi carriers on the road to typhoid elimination in Santiago, Chile, 2017–2019. *J Infect Dis* 2023; **230:** e254–67.

29 Waddington CS, Darton TC, Jones C, et al. An outpatient, ambulant-design, controlled human infection model using escalating doses of *Salmonella* Typhi challenge delivered in sodium bicarbonate solution. *Clin Infect Dis* 2014; **58:** 1230–40.

30 Dobinson HC, Gibani MM, Jones C, et al. Evaluation of the clinical and microbiological response to *Salmonella* Paratyphi A infection in the first paratyphoid human challenge model. *Clin Infect Dis* 2017; **64:** 1066–73.

31 Bavishi C, Dupont HL. Systematic review: the use of proton pump inhibitors and increased susceptibility to enteric infection. *Aliment Pharmacol Ther* 2011; **34:** 1269–81.

32 Bhan MK, Bahl R, Sazawal S, et al. Association between Helicobacter pylori infection and increased risk of typhoid fever. *J Infect Dis* 2002; **186:** 1857–60.

33 Dougan G, Baker S. *Salmonella enterica* serovar Typhi and the pathogenesis of typhoid fever. *Annu Rev Microbiol* 2014; **68:** 317–36.

34 de Jong HK, Parry CM, van der Poll T, Wiersinga WJ. Host-pathogen interaction in invasive salmonellosis. *PLoS Pathog* 2012; **8:** e1002933.

35 Darton TC, Zhou L, Blohmke CJ, et al. Blood culture-PCR to optimise typhoid fever diagnosis after controlled human infection identifies frequent asymptomatic cases and evidence of primary bacteraemia. *J Infect* 2017; **74:** 358–66.

36 Awofisayo-Okuyelu A, McCarthy N, Mgbakor I, Hall I. Incubation period of typhoidal salmonellosis: a systematic review and meta-analysis of outbreaks and experimental studies occurring over the last century. *BMC Infect Dis* 2018; **18:** 483.

37 Balasegaram S, Potter AL, Grynszpan D, et al, and the Typhoid and Paratyphoid Reference Group. Guidelines for the public health management of typhoid and paratyphoid in England: practice guidelines from the National Typhoid and Paratyphoid Reference Group. *J Infect* 2012; **65:** 197–213.

38 Wain J, Diep TS, Ho VA, et al. Quantitation of bacteria in blood of typhoid fever patients and relationship between counts and clinical features, transmissibility, and antibiotic resistance. *J Clin Microbiol* 1998; **36:** 1683–87.

39 Wain J, Pham VB, Ha V, et al. Quantitation of bacteria in bone marrow from patients with typhoid fever: relationship between counts and clinical features. *J Clin Microbiol* 2001; **39:** 1571–76.

40 Van Be Bay P, Wain J, Phuong LT, Ho VA, Hien TT, Parry CM. Quantitative bacterial counts in the bone marrow of Vietnamese patients with typhoid fever. *Trans R Soc Trop Med Hyg* 2022; **116:** 736–44.

41 Edelman R, Levine MM. Summary of an international workshop on typhoid fever. *Rev Infect Dis* 1986; **8:** 329–49.

42 Dunstan SJ, Hue NT, Han B, et al. Variation at HLA-DRB1 is associated with resistance to enteric fever. *Nat Genet* 2014; **46:** 1333–36.

43 Everest P, Wain J, Roberts M, Rook G, Dougan G. The molecular mechanisms of severe typhoid fever. *Trends Microbiol* 2001; **9:** 316–20.

44 Ames WR, Robins M. Age and sex as factors in the development of the typhoid carrier state, and a method for estimating carrier prevalence. *Am J Public Health Nations Health* 1943; **33:** 221–30.

45 Khanam F, Darton TC, Meiring JE, et al. *Salmonella* Typhi stool shedding by patients with enteric fever and asymptomatic chronic carriers in an endemic urban setting. *J Infect Dis* 2021; **224** (suppl 2)**:** S759–63.

46 Srinivasan M, Sindhu KN, Giri S, et al. Salmonella Typhi shedding and household transmission by children with blood culture-confirmed typhoid fever in Vellore, South India. *J Infect Dis* 2021; **224** (suppl 5)**:** S593–600.

47 Dongol S, Thompson CN, Clare S, et al. The microbiological and clinical characteristics of invasive *salmonella* in gallbladders from cholecystectomy patients in Kathmandu, Nepal. *PLoS One* 2012; **7:** e47342.

48 Qureshi S, Maria N, Chawla T, et al. The frequency and associated factors of typhoid carriage in patients undergoing cholecystectomy for gallbladder disease in Pakistan: a cross-sectional study. *PLoS Negl Trop Dis* 2024; **18:** e0011775.

49 Hoffman SA, Sikorski MJ, Levine MM. Chronic Salmonella Typhi carriage at sites other than the gallbladder. *PLoS Negl Trop Dis* 2023; **17:** e0011168.

50 Gal-Mor O. Persistent infection and long-term carriage of typhoidal and nontyphoidal *Salmonellae*. *Clin Microbiol Rev* 2018; **32:** e00088–18.

51 Marchello CS, Hong CY, Crump JA. Global typhoid fever incidence: a systematic review and meta-analysis. *Clin Infect Dis* 2019; **68** (suppl 2)**:** S105–16.

52 Garrett DO, Longley AT, Aiemjoy K, et al. Incidence of typhoid and paratyphoid fever in Bangladesh, Nepal, and Pakistan: results of the Surveillance for Enteric Fever in Asia Project. *Lancet Glob Health* 2022; **10:** e978–88.

53 Meiring JE, Shakya M, Khanam F, et al, and the STRATAA Study Group. Burden of enteric fever at three urban sites in Africa and Asia: a multicentre population-based study. *Lancet Glob Health* 2021; **9:** e1688–96.

54 John J, Bavdekar A, Rongsen-Chandola T, et al, and the NSSEFI Study Team. Burden of typhoid and paratyphoid fever in India. *N Engl J Med* 2023; **388:** 1491–500.

55 Marks F, von Kalckreuth V, Aaby P, et al. Incidence of invasive salmonella disease in sub-Saharan Africa: a multicentre population-based surveillance study. *Lancet Glob Health* 2017; **5:** e310–23.

56 Marks F, Im J, Park SE, et al. Incidence of typhoid fever in Burkina Faso, Democratic Republic of the Congo, Ethiopia, Ghana, Madagascar, and Nigeria (the Severe Typhoid in Africa programme): a population-based study. *Lancet Glob Health* 2024; **12:** e599–610.

57 Kim JH, Choi J, Kim C, et al. Mapping the incidence rate of typhoid fever in sub-Saharan Africa. *PLoS Negl Trop Dis* 2024; **18:** e0011902.

58 Sikorski MJ, Desai SN, Tupua S, et al. Tenacious endemic typhoid fever in Samoa. *Clin Infect Dis* 2020; **71** (suppl 2)**:** S120–26.

59 Jia C, Cao Q, Wang Z, van den Dool A, Yue M. Climate change affects the spread of typhoid pathogens. *Microb Biotechnol* 2024; **17:** e14417.

60 Stuart BM, Pullen RL. Typhoid; clinical analysis of 360 cases. *Arch Intern Med (Chic)* 1946; **78:** 629–61.

61 Parry CM, Hien TT, Dougan G, White NJ, Farrar JJ. Typhoid fever. *N Engl J Med* 2002; **347:** 1770–82.

62 Manesh A, Meltzer E, Jin C, et al. Typhoid and paratyphoid fever: a clinical seminar. *J Travel Med* 2021; **28:** taab012.

63 Azmatullah A, Qamar FN, Thaver D, Zaidi AK, Bhutta ZA. Systematic review of the global epidemiology, clinical and laboratory profile of enteric fever. *J Glob Health* 2015; **5:** 020407.

64 Britto C, Pollard AJ, Voysey M, Blohmke CJ. An appraisal of the clinical features of pediatric enteric fever: systematic review and meta-analysis of the age-stratified disease occurrence. *Clin Infect Dis* 2017; **64:** 1604–11.

65 Aiemjoy K, Tamrakar D, Saha S, et al. Diagnostic value of clinical features to distinguish enteric fever from other febrile illnesses in Bangladesh, Nepal, and Pakistan. *Clin Infect Dis* 2020; **71** (suppl 3)**:** S257–65.

66 Ferreccio C, Levine MM, Manterola A, et al. Benign bacteremia caused by *Salmonella* typhi and paratyphi in children younger than 2 years. *J Pediatr* 1984; **104:** 899–901.

67 Maskey AP, Day JN, Phung QT, et al. *Salmonella enterica* serovar Paratyphi A and *S.* enterica serovar Typhi cause indistinguishable clinical syndromes in Kathmandu, Nepal. *Clin Infect Dis* 2006; **42:** 1247–53.

68 Cruz Espinoza LM, McCreedy E, Holm M, et al. Occurrence of typhoid fever complications and their relation to duration of illness preceding hospitalization: a systematic literature review and meta-analysis. *Clin Infect Dis* 2019; **69** (suppl 6)**:** S435–48.

69 Bhutta ZA. Impact of age and drug resistance on mortality in typhoid fever. *Arch Dis Child* 1996; **75:** 214–17.

70 Parry CM, Thompson C, Vinh H, et al. Risk factors for the development of severe typhoid fever in Vietnam. *BMC Infect Dis* 2014; **14:** 73.

71 Longley AT, Hemlock C, Date K, et al. Illness severity and outcomes among enteric fever cases from Bangladesh, Nepal, and Pakistan: data from the Surveillance for enteric fever in Asia project, 2016–2019. *Clin Infect Dis* 2020; **71** (suppl 3)**:** S222–31.

72 Crump JA, Ramadhani HO, Morrissey AB, et al. Invasive bacterial and fungal infections among hospitalized HIV-infected and HIV-uninfected adults and adolescents in northern Tanzania. *Clin Infect Dis* 2011; **52:** 341–48.

73 Marchello CS, Birkhold M, Crump JA. Complications and mortality of typhoid fever: a global systematic review and meta-analysis. *J Infect* 2020; **81:** 902–10.

74 Pieters Z, Saad NJ, Antillón M, Pitzer VE, Bilcke J. Case fatality rate of enteric fever in endemic countries: a systematic review and meta-analysis. *Clin Infect Dis* 2018; **67:** 628–38.

75 Yu AT, Amin N, Rahman MW, Gurley ES, Rahman KM, Luby SP. Case-fatality ratio of blood culture-confirmed typhoid fever in Dhaka, Bangladesh. *J Infect Dis* 2018; **218** (suppl 4)**:** S222–26.

76 Birkhold M, Coulibaly Y, Coulibaly O, et al. Morbidity and mortality of typhoid intestinal perforation among children in sub-Saharan Africa 1995–2019: a scoping review. *World J Surg* 2020; **44:** 2892–902.

77 Neil KP, Sodha SV, Lukwago L, et al. A large outbreak of typhoid fever associated with a high rate of intestinal perforation in Kasese District, Uganda, 2008–2009. *Clin Infect Dis* 2012; **54:** 1091–99.

78 Sukri L, Banza A, Shafer K, Sanoussi Y, Neuzil KM, Sani R. Typhoid intestinal perforation in Francophone Africa, a scoping review. *PLOS Glob Public Health* 2024; **4:** e0003056.

79 Adamou H, Magagi IA, Habou O, et al. Typhoid intestinal perforation prognostic score in poor-resource settings. *J West Afr Coll Surg* 2023; **13:** 9–17.

80 Birkhold M, Datta S, Pak GD, et al. Characterization of typhoid intestinal perforation in Africa: results from the severe typhoid fever Surveillance in Africa Program. *Open Forum Infect Dis* 2023; **10** (suppl 1)**:** S67–73.

81 Hoffman SL, Punjabi NH, Kumala S, et al. Reduction of mortality in chloramphenicol-treated severe typhoid fever by high-dose dexamethasone. *N Engl J Med* 1984; **310:** 82–88.

82 Rogerson SJ, Spooner VJ, Smith TA, Richens J. Hydrocortisone in chloramphenicol-treated severe typhoid fever in Papua New Guinea. *Trans R Soc Trop Med Hyg* 1991; **85:** 113–16.

83 Lutterloh E, Likaka A, Sejvar J, et al. Multidrug-resistant typhoid fever with neurologic findings on the Malawi–Mozambique border. *Clin Infect Dis* 2012; **54:** 1100–06.

84 Wain J, Hien TT, Connerton P, et al. Molecular typing of multiple-antibiotic-resistant *Salmonella enterica* serovar Typhi from Vietnam: application to acute and relapse cases of typhoid fever. *J Clin Microbiol* 1999; **37:** 2466–72.

85 Pokharel S, White LJ, Aguas R, Celhay O, Pellé KG, Dittrich S. Algorithm in the diagnosis of febrile illness using pathogen-specific rapid diagnostic tests. *Clin Infect Dis* 2020; **70:** 2262–69.

86 Mogasale V, Ramani E, Mogasale VV, Park J. What proportion of *Salmonella* Typhi cases are detected by blood culture? A systematic literature review. *Ann Clin Microbiol Antimicrob* 2016; **15:** 32.

87 Antillon M, Saad NJ, Baker S, Pollard AJ, Pitzer VE. The relationship between blood sample volume and diagnostic sensitivity of blood culture for typhoid and paratyphoid fever: a systematic review and meta-analysis. *J Infect Dis* 2018; **218** (suppl 4)**:** S255–67.

88 Wain J, Diep TS, Bay PV, et al. Specimens and culture media for the laboratory diagnosis of typhoid fever. *J Infect Dev Ctries* 2008; **2:** 469–74.

89 Gasem MH, Keuter M, Dolmans WM, Van Der Ven-Jongekrijg J, Djokomoeljanto R, Van Der Meer JW. Persistence of *Salmonellae* in blood and bone marrow: randomized controlled trial comparing ciprofloxacin and chloramphenicol treatments against enteric fever. *Antimicrob Agents Chemother* 2003; **47:** 1727–31.

90 Nga TV, Karkey A, Dongol S, et al. The sensitivity of real-time PCR amplification targeting invasive *Salmonella* serovars in biological specimens. *BMC Infect Dis* 2010; **10:** 125.

91 Panzner U, Mogeni OD, Adu-Sarkodie Y, et al. Detection of *Salmonella* Typhi nucleic acid by RT-PCR and anti-HlyE, -CdtB, -PilL, and -Vi IgM by ELISA at sites in Ghana, Madagascar and Ethiopia. *BMC Infect Dis* 2022; **22:** 766.

92 Wijedoru L, Mallett S, Parry CM. Rapid diagnostic tests for typhoid and paratyphoid (enteric) fever. *Cochrane Database Syst Rev* 2017; **5:** CD008892.

93 Sapkota J, Hasan R, Onsare R, et al. Comparative analysis of commercially available typhoid point-of-care tests: results of a prospective and hybrid retrospective multicenter diagnostic accuracy study in Kenya and Pakistan. *J Clin Microbiol* 2022; **60:** e0100022.

94 Islam K, Sayeed MA, Hossen E, et al. Comparison of the performance of the TPTest, Tubex, Typhidot and Widal immunodiagnostic assays and blood cultures in detecting patients with typhoid fever in Bangladesh, including using a Bayesian latent class modelling approach. *PLoS Negl Trop Dis* 2016; **10:** e0004558.

95 Davies DH, Jain A, Nakajima R, et al. Serodiagnosis of acute typhoid fever in Nigerian pediatric cases by detection of serum IgA and IgG against haemolysin E and lipopolysaccharide. *Am J Trop Med Hyg* 2016; **95:** 431–39.

96 Kumar S, Nodoushani A, Khanam F, et al. Evaluation of a rapid point-of-care multiplex immunochromatographic assay for the diagnosis of enteric fever. *MSphere* 2020; **5:** e00253–20.

97 Munira SJ, Islam N, Prithe NT, et al. Evaluation of a point-of-care immunochromatographic assay for enteric fever in Dhaka, Bangladesh: a prospective diagnostic accuracy study. *Lancet Microbe* 2025; **6:** 100983.

98 Blohmke CJ, Muller J, Gibani MM, et al. Diagnostic host gene signature for distinguishing enteric fever from other febrile diseases. *EMBO Mol Med* 2019; **11:** e10431.

99 Näsström E, Parry CM, Vu Thieu NT, et al. Reproducible diagnostic metabolites in plasma from typhoid fever patients in Asia and Africa. *eLife* 2017; **6:** e15651.

100 Lin FY, Becke JM, Groves C, et al. Restaurant-associated outbreak of typhoid fever in Maryland: identification of carrier facilitated by measurement of serum Vi antibodies. *J Clin Microbiol* 1988; **26:** 1194–97.

101 Gupta A, My Thanh NT, Olsen SJ, et al. Evaluation of community-based serologic screening for identification of chronic *Salmonella* typhi carriers in Vietnam. *Int J Infect Dis* 2006; **10:** 309–14.

102 Charles RC, Sultana T, Alam MM, et al. Identification of immunogenic *Salmonella enterica* serotype Typhi antigens expressed in chronic biliary carriers of *S.* Typhi in Kathmandu, Nepal. *PLoS Negl Trop Dis* 2013; **7:** e2335.

103 Näsström E, Jonsson P, Johansson A, et al. Diagnostic metabolite biomarkers of chronic typhoid carriage. *PLoS Negl Trop Dis* 2018; **12:** e0006215.

104 WHO. Model list of essential medicines: typhoid fever. https://list.essentialmeds.org/?indication=219 (accessed July 11, 2025).

105 Nabarro LE, McCann N, Herdman MT, et al. British infection association guidelines for the diagnosis and management of enteric fever in England. *J Infect* 2022; **84:** 469–89.

106 McCann N, Nabarro L, Morris-Jones S, et al. Outpatient management of uncomplicated enteric fever: a case series of 93 patients from the Hospital for Tropical Diseases, London. *J Infect* 2022; **85:** 397–404.

107 Effa EE, Lassi ZS, Critchley JA, et al. Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever). *Cochrane Database Syst Rev* 2011; **2011:** CD004530.

108 Eliakim-Raz N, Lador A, Leibovici-Weissman Y, Elbaz M, Paul M, Leibovici L. Efficacy and safety of chloramphenicol: joining the revival of old antibiotics? Systematic review and meta-analysis of randomized controlled trials. *J Antimicrob Chemother* 2015; **70:** 979–96.

109 Kuehn R, Stoesser N, Eyre D, Darton TC, Basnyat B, Parry CM. Treatment of enteric fever (typhoid and paratyphoid fever) with cephalosporins. *Cochrane Database Syst Rev* 2022; **11:** CD010452.

110 Britto CD, Wong VK, Dougan G, Pollard AJ. A systematic review of antimicrobial resistance in *Salmonella enterica* serovar Typhi, the etiological agent of typhoid. *PLoS Negl Trop Dis* 2018; **12:** e0006779.

111 Qamar FN, Yousafzai MT, Dehraj IF, et al. Antimicrobial resistance in typhoidal *Salmonella*: Surveillance for Enteric Fever in Asia Project, 2016–2019. *Clin Infect Dis* 2020; **71** (suppl 3)**:** S276–84.

112 Marchello CS, Carr SD, Crump JA. A systematic review on antimicrobial resistance among *Salmonella* Typhi worldwide. *Am J Trop Med Hyg* 2020; **103:** 2518–27.

113 Herdman MT, Karo B, Dave J, et al. Increasingly limited options for the treatment of enteric fever in travellers returning to England, 2014–2019: a cross-sectional analytical study. *J Med Microbiol* 2021; **70:** 001359.

114 Posen HJ, Wong W, Farrar DS, et al. Travel-associated extensively drug-resistant typhoid fever: a case series to inform management in non-endemic regions. *J Travel Med* 2023; **30:** taac086.

115 Ashton PM, Chunga Chirambo A, Meiring JE, et al, and the STRATAA Study Group. Evaluating the relationship between ciprofloxacin prescription and non-susceptibility in *Salmonella* Typhi in Blantyre, Malawi: an observational study. *Lancet Microbe* 2024; **5:** e226–34.

116 Sajib MSI, Tanmoy AM, Hooda Y, et al. Tracking the emergence of azithromycin resistance in multiple genotypes of typhoidal *Salmonella*. *MBio* 2021; **12:** e03481–20.

117 Carey ME, Jain R, Yousuf M, et al. Spontaneous emergence of azithromycin resistance in independent lineages of *Salmonella* Typhi in Northern India. *Clin Infect Dis* 2021; **72:** e120–27.

118 Duy PT, Dongol S, Giri A, et al. The emergence of azithromycin-resistant *Salmonella* Typhi in Nepal. *JAC Antimicrob Resist* 2020; **2:** dlaa109.

119 Qamar FN, Yousafzai MT, Khalid M, et al. Outbreak investigation of ceftriaxone-resistant *Salmonella enterica* serotype Typhi and its risk factors among the general population in Hyderabad, Pakistan: a matched case-control study. *Lancet Infect Dis* 2018; **18:** 1368–76.

120 Klemm EJ, Shakoor S, Page AJ, et al. Emergence of an extensively drug-resistant *Salmonella enterica* serovar Typhi clone harboring a promiscuous plasmid encoding resistance to fluoroquinolones and third-generation cephalosporins *MBio* 2018; **9:** e00105-18.

121 Qureshi S, Naveed AB, Yousafzai MT, et al. Response of extensively drug resistant *Salmonella* Typhi to treatment with meropenem and azithromycin, in Pakistan. *PLoS Negl Trop Dis* 2020; **14:** e0008682.

122 Argimón S, Nagaraj G, Shamanna V, et al. Circulation of third-generation cephalosporin resistant *Salmonella* Typhi in Mumbai, India. *Clin Infect Dis* 2022; **74:** 2234–37.

123 Samajpati S, Pragasam AK, Mandal S, Balaji V, Dutta S. Emergence of ceftriaxone resistant *Salmonella enterica* serovar Typhi in Eastern India. *Infect Genet Evol* 2021; **96:** 105093.

124 Akshay SD, Upadhyaya H, Shukla N, et al. Comprehensive analysis of extensive drug-resistant *Salmonella* Typhi in Gujarat region, India: genomic findings and prospective alternative therapy. *Microbiol Spectr* 2025; **13:** e0254024.

125 Thirumoorthy T, Jacob J, SR, et al. Recent emergence of carbapenem-resistant *Salmonella* Typhi in India: resistance profile and phylogenetic analysis. European Society of Clinical Microbiology and Infectious Diseases Global, Vienna, Austria; April 11–15, 2025 (abstract P1404).

126 Sajib MSI, Tanmoy AM, Hooda Y, et al. Trends in antimicrobial resistance amongst *Salmonella* Paratyphi A isolates in Bangladesh: 1999–2021. *PLoS Negl Trop Dis* 2023; **17:** e0011723.

127 Zmora N, Shrestha S, Neuberger A, et al. Open label comparative trial of mono versus dual antibiotic therapy for Typhoid Fever in adults. *PLoS Negl Trop Dis* 2018; **12:** e0006380.

128 Giri A, Karkey A, Dongol S, et al. Azithromycin and cefixime combination versus azithromycin alone for the out-patient treatment of clinically suspected or confirmed uncomplicated typhoid fever in south Asia: a randomised controlled trial protocol. *Wellcome Open Res* 2021; **6:** 207.

129 Parry CM, Qamar FN, Rijal S, McCann N, Baker S, Basnyat B. What should we be recommending for the treatment of enteric fever? *Open Forum Infect Dis* 2023; **10** (suppl 1)**:** S26–31.

130 Butler T, Knight J, Nath SK, Speelman P, Roy SK, Azad MA. Typhoid fever complicated by intestinal perforation: a persisting fatal disease requiring surgical management. *Rev Infect Dis* 1985; **7:** 244–56.

131 Contopoulos-Ioannidis DG, Ioannidis JP. Claims for improved survival from systemic corticosteroids in diverse conditions: an umbrella review. *Eur J Clin Invest* 2012; **42:** 233–44.

132 McCann N, Scott P, Parry CM, Brown M. Antimicrobial agents for the treatment of enteric fever chronic carriage: a systematic review. *PLoS One* 2022; **17:** e0272043.

133 WHO. Typhoid vaccines: WHO position paper—March 2018. March 30, 2018. https://www.who.int/publications/i/item/who-wer9313 (accessed July 11, 2025).

134 Im J, Khanam F, Ahmmed F, et al. Prevention of typhoid fever by existing improvements in household water, sanitation, and hygiene, and the use of the Vi polysaccharide typhoid vaccine in poor urban slums: results from a cluster-randomized trial. *Am J Trop Med Hyg* 2022; **106:** 1149–55.

135 Wolf J, Hubbard S, Brauer M, et al. Effectiveness of interventions to improve drinking water, sanitation, and handwashing with soap on risk of diarrhoeal disease in children in low-income and middle-income settings: a systematic review and meta-analysis. *Lancet* 2022; **400:** 48–59.

136 Milligan R, Paul M, Richardson M, Neuberger A. Vaccines for preventing typhoid fever. *Cochrane Database Syst Rev* 2018; **5:** CD001261.

137 WHO. Prequalified vaccines. https://extranet.who.int/prequal/vaccines/prequalified-vaccines (accessed July 11, 2025).

138 Qadri F, Khanam F, Liu X, et al. Protection by vaccination of children against typhoid fever with a Vi-tetanus toxoid conjugate vaccine in urban Bangladesh: a cluster-randomised trial. *Lancet* 2021; **398:** 675–84.

139 Shakya M, Voysey M, Theiss-Nyland K, et al, and the TyVAC Nepal Team. Efficacy of typhoid conjugate vaccine in Nepal: final results of a phase 3, randomised, controlled trial. *Lancet Glob Health* 2021; **9:** e1561–68.

140 Patel PD, Liang Y, Meiring JE, et al, and the TyVAC team. Efficacy of typhoid conjugate vaccine: final analysis of a 4-year, phase 3, randomised controlled trial in Malawian children. *Lancet* 2024; **403:** 459–68.

141 Patel PD, Liang Y, Meiring JE, et al, and the TyVAC team. Efficacy of typhoid conjugate vaccine: final analysis of a 4-year, phase 3, randomised controlled trial in Malawian children. *Lancet* 2024; **403:** 459–68.

142 Qadri F, Khanam F, Zhang Y, et al. 5-year vaccine protection following a single dose of Vi-tetanus toxoid conjugate vaccine in Bangladeshi children (TyVOID): a cluster randomised trial. *Lancet* 2024; **404:** 1419–29.

143 Khanam F, Babu G, Rahman N, et al. Immune responses in children after vaccination with a typhoid Vi-tetanus toxoid conjugate vaccine in Bangladesh. *Vaccine* 2023; **41:** 3137–40.

144 Shaum A, Mujuru HA, Takamiya M, et al. Enhanced surveillance for adverse events following immunization during the 2019 typhoid conjugate vaccine campaign in Harare, Zimbabwe. *Vaccine* 2022; **40:** 3573–80.

145 Russell AL, Hampton LM, Sinha A, Luquero FJ, Abdelwahab J. Progress in the typhoid conjugate vaccine program rollout supported by GAVI during the COVID-19 pandemic and the path forward. *Open Forum Infect Dis* 2023; **10** (suppl 1)**:** S13–16.

146 Raqib R. Bivalent conjugate vaccines for typhoid and paratyphoid fever. *Lancet* 2024; **403:** 1516–17.

147 Mather RG, Hopkins H, Parry CM, Dittrich S. Redefining typhoid diagnosis: what would an improved test need to look like? *BMJ Glob Health* 2019; **4:** e001831.

148 Khanam F, Ross AG, McMillan NAJ, Qadri F. Toward typhoid fever elimination. *Int J Infect Dis* 2022; **119:** 41–43.

Copyright © 2025 Elsevier Ltd. All rights reserved, including those for text and data mining, AI training, and similar technologies.